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Instructive selection and immunological theory

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Immunological Reviews 2002
Vol 185: 50–53

Immunological Reviews
0105-2896

Summary: The turning point of modern immunological theory was the advent of the clonal selection theory (Burnet, Talmage – 1957). A useful heuristic in the classification of theoretical models was the contrast of 'instructive' with 'selective' models of the acquisition of information by biological systems. The neo-Darwinian synthesis of the 1940s had consolidated biologists' model of evolution based on prior random variation and natural selection, viz. differential fecundity. While evolution in the large was by then pretty well settled, controversy remained about examples of cellular adaptation to chemical challenges, like induced drug-resistance, enzyme formation and the antibody response. While instructive theories have been on the decline, some clear cut examples can be found of molecular imprinting in the abiotic world, leading, e.g. to the production of specific sorbents. Template-driven assembly, as in DNA synthesis, has remained a paradigm of instructive specification. Nevertheless, the classification may break down with more microscopic scrutiny of the processes of molecular fit of substrates with enzymes, of monomers to an elongating polymer chain, as the reactants often traverse a state space from with activated components are appropriately selected. The same process may be 'instructive' from a holistic, 'selective' from an atomic perspective.

'The universe (which others call the library) is composed of an indefinite and perhaps infinite number of hexagonal galleries with vast air shafts between, surrounded by very low railings. From any of the hexagons one can see, interminably, the upper and lower floors . . .'

So begins a short story 'The Library of Babel' (1), by the Argentinian writer Jorge Luis Borges, where he showed that all knowledge can be reduced to a problem of selection. His library of infinite dimensions was filled with books printed in an obscure code in which familiar phrases occasionally appeared. Eventually, a mathematician-inhabitant of this space surmised that each book was one of all possible random concatenations of letters. After a few centuries of cultural despair, the inhabitants were inspired by a new revelation – that the library must in fact contain all knowledge – and every possible fallacy.

The problem was merely one of selecting the proper texts.

Prior to the advent of clonal selection (2–5) the reigning imagery of the specific immune response was that of the foundry or mint, as if the antibodies were coins struck from the antigen as die (6). This concept's prestige had been greatly boosted by Linus Pauling's endorsement of claims that controlled denaturation and renaturation of serum globulin in the presence of a polysaccharide antigen resulted in specifically reactive modified globulins (7, 8).

Starting with Jerne in 1955 (9), clonal selection counterproposals asserted that all the requisite diversity was already represented in some population of biological units, the antigen then having the role of specific interaction with and activation of the selected units. In his original formulation, Jerne was less than credible, as he presupposed autoreplication of the antibody globulin molecules themselves. I toyed with the idea of some equally numerous but more sophisticated intracellular particles – I might have anachronistically called them ribosomes. All fell into place with Burnet and Talmage's insight that lymphocytic cells were already numerous enough to qualify, the idea of their hypermutability compared to other somatic cells being a small burden. This idea required a critical look at the prevalent notion that the diversity of antibodies was infinite, vs. merely very large.

In 1959, I published (4) a restatement of clonal selection within the dogma of the DNA > RNA > protein-sequence axis: genetic diversification (mutation) > transcription > translation followed by spontaneous folding of the polypeptide chain into the conformation prespecified by the sequence. Seeking to generalize distinctions about mechanisms of information transfer in biological systems, I introduced the dichotomy of 'instructive' vs. 'elective' mechanisms. (Perhaps misguidedly, I reserved 'selective' for that subset of 'elective' that entailed differential reproduction, as in Darwinian natural selection. That subtlety has been all but ignored.) How have these tropes fared during the past four decades (10)?

In quest of examples of instructive mechanism, to start with, Pauling's idea of die-coinage has indeed been substantiated in nonbiological systems. His student Frank Dickey (11) initiated a line of research that has burgeoned into a small industry of 'molecular imprinting', in which specific sorbents can be manufactured from a variety of polymers assembled in the presence of molecular templates (12). This process can also be applied to re-conformation of polypeptides, though this procedure works well only in nonaqueous media (13). In biological systems, we have the role of chaperones guiding the 'proper' folding of newly assembled or heat-stressed polypeptides, though this entails very limited specificity. More critical is the enigma of the prion, how, according to Prusiner's theory (14), a pathogenic conformation of PrP-scrapie can re-conform the normal PrP-cellular precursor into its own malignant image. Our interpretations have the burden of accounting for diverse strains of prions in a given host species.

The instructional simile, of course, is central to cultural transmission of song, speech, text, figuration of all kinds involving both mimicry of and abstraction and codification of the lesson. We know nothing of the intimate neurobiological mechanisms, frustrating anything more that I might have to say. The contrast of instruction vs. selection remains a powerful conceptual tool. The naive may often need a reminder of how powerful selection can be in the shaping of outcomes, despite the pervasive evidence of phylogeny itself (15). In most people's minds today, the paradigm of biological instructive information must be the DNA (or RNA) sequence, daughter chromosomes having received millions of bits of information in faithful acquiescence to the teaching of the parental DNA sequence.

But let us look more closely at biological DNA replication, and its near cousin enzymatic catalysis, though they seem at first glance to be unabashedly instructive. We often say that an enzyme 'causes' a given metabolic transformation to take place. Look more closely in the black box, and we can invent a more ambiguous formulation: the enzyme and the substrate both traverse a state space in which activated conformations occur 'spontaneously', perhaps in several steps, and each may be stabilized by interaction with the other ligand. With respect to template-driven assembly of DNA, each step of elongation is a trial of fit of the next nucleotide; there is ordinarily a second stage of exonuclease editing which selectively prunes any misfit addends. In these cases, it may well be said that the judgment of selective vs. instructive depends on the power of the microscope trained on the black box. The heuristic value of the dichotomy may be in forcing a reconsideration of the pervasiveness of selective mechanisms, even for what appear at first sight to be blatant instruction.

Instructionist imagery is first cousin to the quasi-Lamarckian paradigm that specific environments might induce heritable genetic changes. (I say quasi in deference to Ernst Mayr's (15) caution that Lamarck made no such claim; what he said was that animals might inherit the physiological responses they learned in the course of adaptation to the environment.) Early microbiologists readily convinced themselves that antibiotics induced resistance in bacterial cultures. We use that expression today; after all the evidence is clearly manifest: 'Add an antibiotic to a microbial culture *in vitro* or in the

environment and behold in a short time the emergence of resistance'. Accordingly, Luria (16) described this as the last foothold of Lamarckian thinking. It has been essentially put to rest by focusing the microscope inside the black box (or test tube) and examining the competition within the respondent population – in which a minute fraction of resistant organisms can be discerned prior to adding the antibiotic. So, here, the Darwinian dogma has prevailed, though complicated in the details of what we mean by purely random mutagenesis (17–19). Correspondingly, selective apoptosis has been invoked as a major epigenetic modality in organ formation, most famously in the delineation of the digits in limb development (20) and other developmental processes like memory (reviewed in 10). This process can also be thought of as selective retention. Obviously, any pattern can be reduced to some number of pixels, overlain by a mask of 0 s and 1 s.

Darwinian imagery has also permeated informatic technology, in forms like genetic algorithms. One example of automated inference, DENDRAL (21), prospectively generates a space of potential solutions to problems of mass-spectral structure determination, all possible organic molecules – a catalog akin to Borges' Library. Domain knowledge is then used for selective pruning of the tree-generator, the earlier the better, to cone down the inferences to those compatible with the data. Automated programming seeks to discover algorithms by a related process. In this case a generator that randomly manipulates primitive bits is rapidly defeated. Calling upon analogies from biological evolution, more successful systems (22) develop hierarchies of functional modules. These are then the units of incremental mutation, or often more productively of hybridization and reassortment. As pointed out by Herbert Simon (23), such modularization is all but imperative for smooth epigenesis or for evolution of complex systems – else almost any mutation or environmental disturbance would be lethal. Under the label of 'combinatorial optimization', such processes are bedeviled by perplexities of assessing strategic progress, of avoiding being stuck on a local optimum, of getting round the reality that progress is not always monotonic by the parochial measures accessible to us. Similar lessons face us in the understanding of the immunological response.

To turn to another bemusement entirely, I have often asked myself what might be the most primitive exemplar of adaptive immunity, possible precursors of the machinery we have inherited from our piscine ancestors. A candidate I now put forward is the production of soluble phage receptors by bacteria, which can efficiently neutralize phages, e.g. in Shigella (24, 25). In principle, a mutation in specificity of the phage ligand would restore bacterial vulnerability, and in turn selectively promote bacterial mutant receptor strains that restored neutralizing capacity. The problem is that since Burnet and Goebel (21, 22), soluble receptors have remained a laboratory artefact (along with much other phage lore) and I am aware of no investigation as to their role in the natural history of bacterial/viral relationships.

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